REMARKS

Reconsideration is requested.

Claims 1-91, 93, 135 and 147-151 have been canceled, without prejudice.

Claims 92, 94-134 and 136-146 are pending. Claim 125 has been rewritten in independent form, in view of the Examiner's indication that claims 125 and 126 (which is dependent from claim 125) contain allowable subject matter. Allowance of at least claims 125 and 126 is requested.

Claims 92 and 146 have been revised, without prejudice, to further describe R^1 in a manner disclosed on page 25, lines 15-16 and 20-21, and page 26, lines 23-24. No new matter has been added.

Claim 122 has been revised, without prejudice, to obviate the Section 112, second paragraph, rejection to same. Withdrawal of the rejection is requested.

Clarification is requested regarding the Examiner's reference to claims 1, 2, 3, 6, 13, 14 and 17 on page 3 of the Office Action dated January 6, 2010 as the noted claims were canceled, without prejudice, in a Supplemental Amendment filed August 27, 2007.

The Section 102 rejection of claims 92, 99, 100-105, 108-121 and 124 over Slotte et al (Biochemistry (1993), 32(31), 7886-92) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following.

The Examiner's characterization of cholesterol as a drug is not supported by evidence of record. One of ordinary skill will appreciate, for example, that drugs are

generally distinguished from endogenous biochemicals by being introduced from outside the organism.

Moreover, the revision to claim 92 above further distinguishes the claims over the cited art in the recitation of an amphiphilic drug. The term “amphiphilic”, which will be appreciated by one of ordinary skill in the art, is also defined at page 9, lines 12-14 of the description as follows.

> The terms "amphiphilic" and "amphipathic" are used herein interchangeably, and are used in the conventional sense to mean compounds (e.g., drugs) which are both (i) hydrophilic and (ii) hydrophobic (e.g., lipophilic).

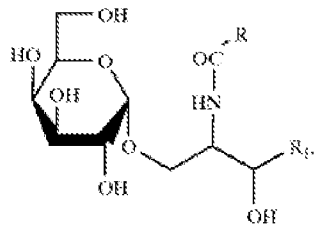
One of ordinary skill in the art will appreciate that cholesterol is not an amphiphilic drug according to the claims.

Withdrawal of the Section 102 rejection based on Slotte et al. is requested.

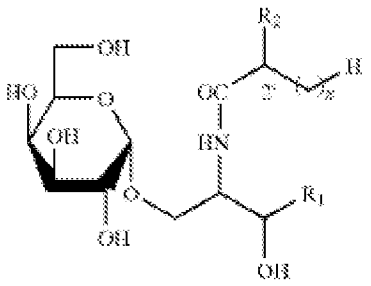
The Section 103 rejection of claims 92-121 and 135-146 over Higa et al (U.S. Patent No. 5,936,076) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

On pages 4-6, the Examiner has argued that many of the previous claims are obvious in view of Higa et al.

Higa et al. describes a certain class of α-galactoceramides of the following formula, which apparently have anti-tumour activity and immuno-stimulating activity (see, e.g., column 1, lines 11-14). All of the compounds have an α-D-galactosyl head group, which is believed to be responsible for the reported biological activity:



Furthermore, the focus of Higa et al. is on "long-chain" α-D-galactosyl sphingolipids wherein the R group is a "long-chain" group. See for example, compounds of the following formula (I) of the cited patent:



(I)

wherein x preferably is 8-22 with the substituents described in ¶(a) in column 4 of the patent; or wherein x denotes 18-26 or preferably 21-25 with the substituents described in ¶(b) in column 4 of the patent; or wherein x denotes 20-24 or preferably 21-23 with the substituents described in ¶(c) in column 4 of the patent; or wherein x denotes 10-18 or preferably 11-17 with the substituents described in ¶(d) in column 4 of the patent; or wherein x denotes 21-25 or preferably 22-24 with the substituents described in ¶(e) in column 4 of the patent. Similar long chain substituents are described by the remaining general formulas of the cited patent. The applicants note that where R_2 of the compounds of the cited patent is other than H, the value of x of the

formulas of the cited patent are greater than or equal to 18. See for example, column 4, lines 34-35; column 4, lines 43-44; column 4, lines 52-53; column 4, lines 56-57; column 4, lines 64-65; column 5, lines 34-35; column 5, lines 38-39; column 5, lines 44-45; column 5, line 51; column 6, line 39; column 6, line 59; column 7, line 48; column 7, line 51; column 7, line 66; and column 8, line 16.

The cited art fails to suggest the formulation of short-chain sphingolipids of the claims.

Withdrawal of the Section 103 rejection based on Higa is requested.

The Section 103 rejection of claims 92, 99-121 and 123 over Elias et al (U.S. Patent No. 6,054,433) is traversed. Reconsideration and withdrawal of the Section 103 rejection are requested in view of the following distinguishing remarks.

The Elias et al. technology is apparently based on the observation that "the exposure of mammalian epithelial tissues to inhibitors of β-glucocerebrosidase resulted in improved skin thickness, smoothness, flexibility and contour" and that "exogenously added glucosylceramide increased the rate of DNA synthesis and DNA content in cultured keratinocyte cells. (See, e.g., column 4, lines 35-39 and lines 56-58.)

Accordingly, Elias et al. describes compositions and methods "effective to stimulate epithelial cell proliferation and/or enhance epithelial moisturization and lubrication in a mammalian subject" (see, e.g., the abstract). The compositions comprise, for example, an inhibitor of β-glucosidase (e.g., β-glucocerebrosidase) activity; a glycosphingolipid; or a combination thereof (see column 1, lines 17-21).

The Examiner has asserted the following, at page 7 of the Office Action dated January 6, 2010:

> It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, to prepare a composition comprising a combination of the inhibitors of such as N-octanoylglucosylsphingosine and bromoconduritol-B-epoxide to stimulate epithelial cell proliferation and/or enhance epithelial moisturization and lubrication in a mammalian subject, since Elias et al. disclose that the said compounds can be used and in addition the combination of compounds that are used to treat the same diseases are well known in the art. More specifically, it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

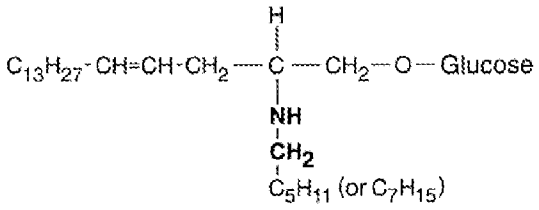
The Examiner is understood to be asserting that, with Elias et al. in hand, the ordinarily skilled person would have been motivated to have prepared a composition comprising (a) N-octanoylglucosylsphingosine and (b) bromoconduritol-B-epoxide ("a drug").

The first component, "N-octanoylglucosylsphingosine" is discussed in Elias et al. at column 8, lines 27-38.

> "In addition, N-acylglucosylsphingosine (sphingosine group varies from C14 to C22, with varying degrees of unsaturation and hydroxylation; acyl groups vary from C2 to C30) and related compounds are potent competitive inhibitors of β-glucocerebrosidase. The most effective acyl groups are the N-hexyl and N-octanoyl compounds, N-hexylglucosylsphingosine and N-octanoylglucosylsphingosine (Radin, N. S. et al., supra). These secondary amines eliminate the carbonyl (C=O)

> group from the N-acyl group on the ceramide backbone, substituting for the amide group (compare FIG. 4 with FIG. 5) in the normal ceramide backbone+glucose."

The first component, "N-octanoylglucosylsphingosine" is illustrated in Figure 4 therein and reproduced as follows:



This first component, "N-octanoylglucosylsphingosine", is not a "short-chain sphingolipid" as defined in the pending claims. The "N-octanoylglucosylsphingosine" of the cited patent is a secondary amine and not an amide, as required by the presently claimed invention. The "N-octanoylglucosylsphingosine" of the cited art does not have a -C(=O)- group as found in the "short-chain sphingolipid" defined in the pending claims.

Therefore, even if the ordinarily skilled person would have been motivated to act as the Examiner suggests (which the applicant does not admit), the result would not have been within the scope of the pending claims.

Furthermore, all of the Elias et al. examples of "compositions" are compositions for topical administration. For example, Examples 1, 3, and 4 describe preparation of a "gel". Example 2 describes preparation of an "ointment". Similarly, all of the Elias et al. examples of "administration" are topical. For example, Examples 10, 11, and 13, compositions were "applied...to intact hairless mouse skin". In Example 12, "the

epidermis of a hairless mouse was treated" with the compositions. In Example 14, "mice were treated topically" with the compositions.

With Elias et al. in hand, the ordinarily skilled person would not have been motivated to formulate compositions described therein as "a pharmaceutical composition suitable for parenteral administration", as required by the claims.

The pending claims are inventive in view of Elias et al. and withdrawal of the Section 103 rejection based on same is requested.

The Section 103 rejection of claims 92, 99-102, 105, 108-117, 127-131 and 135-146 over Futerman et al (Methods in Enzymology (1992), 209 (Phospholipid Biosynth.), 437-46) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Futerman et al. describes methods and reagents (specifically, sphingolipids) for studying the metabolism and intracellular translocation of lipids in cultured cells. The study shows, inter alia, that sphingolipids which bear a short-chain (such as the "GlyCer" shown in Figure 1 on page 439 therein) "spontaneously transfer from either protein complexes or liposomes into biological membranes without destroying membrane integrity" (see page 438 therein). This rapid and spontaneous transfer and insertion has "proved useful in determining the sites and topology of sphingolipid synthesis and degradation" (see page 443 therein).

The "Conclusion" of Futerman et al., on pages 445-446 therein, states:

> "An advantage of using *N*-([1-^{14}C]hexanoyl)sphingolipids to assay sphingolipid metabolism is their ability to rapidly and spontaneously insert into biological membranes without destroying membrane integrity. This property allows analysis of the activity of enzymes of sphingolipid metabolism under conditions in which the rate of product formation is not limited by availability of substrate, as is often the case with naturally occurring lipids whose rates of spontaneous transfer are extremely slow. Thus, the use of *N*-([1-^{14}C]hexanoyl)sphingolipids provides an alternative means for studying sphingolipid metabolism in vitro." (emphasis added)

Futerman et al. provides motivation to use certain short-chain spingolipids (e.g., "GlcCer" in Figure 1 therein) to study sphingolipid metabolism in vitro.

The Examiner has asserted the following, at pages 8-9 of the Office Action dated January 6, 2010:

> "It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, to prepare a composition comprising a combination of Futherman et al.'s compound and a drug such as a protein complex or liposome in order to use it to investigate or study the transfer of Futherman et al's compound from either protein complexes or liposomes into biological membranes without destroying membrane integrity and to study sphingolipid metabolism in tissue the sphingolipid metabolism in tissue.
>
> One having ordinary skill in the art would have been motivated in view of Futerman et al. to prepare a composition comprising a combination of Futherman et al.'s compound and a drug such as a protein complex or liposome in order to use it to investigate or study the transfer of Futherman et al's compound from either protein complexes or liposomes into biological membranes without destroying membrane integrity and to study sphingolipid metabolism in tissue the sphingolipid metabolism in tissue."

The Examiner appears to have suggested that it would have allegedly been obvious to prepare and use a composition comprising both Futerman's short-chain sphingolipid (e.g., "GlcCer" in Figure 1 therein) and "a drug such as a protein complex or liposome" in order to "investigate or study the transfer of Futherman et al's compound from either protein complexes or liposomes into biological membranes without destroying membrane integrity and to study sphingolipid metabolism in tissue the sphingolipid metabolism in tissue".

The Examiner's unsupported assertions fail to establish a *prima facie* case of obviousness.

There is no motivation in the cited art for the ordinarily skilled person to have done as the Examiner suggests.

Futerman et al. provides motivation to use certain short-chain spingolipids to study sphingolipid metabolism in vitro. These spingolipids rapidly and spontaneously insert into biological membranes without destroying membrane integrity. This property allows spingolipids (e.g., radio-labelled sphingolipids) to be studied, in situ, in a membrane. This is especially useful when studying spingolipid metabolism.

Futerman et al. describes how these sphingolipids can be delivered to the membrane (for insertion) either "complexed with defatted serum albumin" or "incorporated into unilamellar liposomes" (see page 440 therein).

Nothing in Futerman et al. would have led the ordinarily skilled person to contemplate adding a drug to the delivery vehicle, as asserted by the Examiner.

Moreover, Futerman et al. is focused on in vitro studies of sphingolipid metabolism. One of ordinary skill would not have made the claimed invention from the disclosure of Futerman et al. The pending claims are inventive in view of Futerman et al. and withdrawal of the Section 103 rejection based on same is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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